A Randomized Controlled Trial of High-Dose Maintenance Interferon Therapy in Chronic Hepatitis C

Vito Di Marco[1], Oreste Lo Iacono[1], Calogero Camma[3], Piero L. Almasio[1], Alessandra Vaccaro[2], Patrizia Fuschi[1], Marco Giunta[2], Carmelo Fabiano[2], Luigi Pagliaro[2], and Antonio Craxi[1]*

[1]*Clinica Medica I, Palermo, Italy*
[2]*Istituto di Medicina Generale e Pneumologia, University of Palermo, Palermo, Italy*
[3]*ISMEDA, Consiglio Nazionale delle Ricerche, Palermo, Italy*

In chronic hepatitis C virus (HCV) infection, the rate of sustained response to interferon is low. We evaluated, in patients responding to a 26-week course of interferon, the effect of high-dose maintenance therapy in preventing relapse. Three hundred and ten patients with chronic HCV infection (38.3% with cirrhosis, 80.6% with HCV type 1) received interferon alfa-2b for 26 weeks (10 MU tiw for 8 weeks, then 5 MU tiw for 18 weeks). One hundred and twenty-four subjects (40%) normalized aminotransferases, and were allocated randomly either to continue on 5 MU tiw for a further 26 weeks (prolonged therapy group: 60 patients) or to stop interferon (brief therapy group: 64 patients).

Fifty-two weeks after stopping interferon the overall sustained biochemical response rate was 13.2% (41/310). The number of patients with normal aminotransferases was comparable between the prolonged and brief therapy groups (30% vs. 35.9%, P = n.s.), and the rate of HCV-RNA clearance was similar (48.8% vs. 42.4%, P = n.s.). The timing of posttreatment relapse was not influenced by the duration of therapy. Fifty-nine patients (19%) did not complete therapy due to adverse effects. Multivariate analysis identified four features predicting sustained biochemical response in subjects normalizing aminotransferases under therapy: negative HCV-RNA at end of therapy, normal aminotransferases at 4 weeks of therapy, high baseline aminotransferases, and high baseline platelets. Infection with HCV type 1 was not a significant predictor of response, due to its high prevalence in our population (80.6%).

It is concluded that in patients with chronic hepatitis C mostly infected by HCV type 1, a prolonged high-dose interferon course (900 MU over 52 weeks) did not increase the rate of sustained biochemical response and of HCV-RNA clearance in comparison to a brief course (510 MU over 26 weeks). ***J Med Virol 51:17–24, 1997.***

KEY WORDS: interferon therapy; chronic hepatitis; HCV; prolonged high dose; sustained response; cirrhosis; genotype

INTRODUCTION

Interferon (IFN) treatment is effective in normalizing aminotransferases (ALT) in chronic hepatitis C virus (HCV) infection [Tine et al., 1991]. However, only a minority of patients are cured permanently. Only 10–25% of all IFN-treated patients have a sustained response to the standard schedule (3 MU tiw for 26 weeks) [Di Bisceglie et al., 1989; Davis et al., 1989; Jouet et al., 1994; Chemello et al., 1995]. Several randomized clinical trials have been carried out to define the optimal schedule(s) of treatment. Some clinical trials evaluated higher doses [Iino et al., 1993; De Bac et al., 1993; Hagiwara et al., 1993; Matsumoto et al., 1994], and others longer periods of treatment [Camps et al., 1993a; Caporaso et al., 1993; Diodati et al., 1994; Lin et al., 1995; Poynard et al., 1995b]. Available evidence suggests that the current schedule might be suboptimal in respect to the likelihood of primary response (normal ALT at the end of therapy), and that higher doses (6 MU tiw) might be more effective [Poynard et al., 1995a; Niederau et al., 1995]. Also, prolonging therapy at the standard dose of 3 MU tiw up to 52 or even 78 weeks seems to increase the rate of sustained response, with-

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*Correspondence to: Prof. Antonio Craxi, Divisione di Medicina Generale e Gastroenterologia, Cattedra di Medicina Interna (C.L.O.), Piazza delle Cliniche 2, 90127 Palermo, Italy.

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out achieving any increase in primary response [Poynard et al., 1995b].

In a large cohort of subjects with community-acquired chronic HCV infection, mostly infected by HCV type 1b [Magrin et al., 1994], we undertook a trial of high-dose, protracted IFN treatment. A comparison between brief and prolonged treatment was made by randomizing responders at 26 weeks to stop IFN or to continue with a further 26 weeks of maintenance therapy.

The main aim of this study was to assess whether continuing IFN therapy at a relatively high dose in subjects who have normalized ALT under treatment will consolidate biochemical and virological response. Secondary aims were to identify features predictive of a high likelihood of sustained response, and to verify the tolerability and safety of the schedule.

PATIENTS AND METHODS

Patients

Three hundred and ten consecutive patients admitted to our department between October 1989 and January 1992 were studied. All subjects who entered the trial were aged between 18 and 60 years, their ALT was at least twice the upper normal limits for at least 6 months, they were anti-HCV positive, and they had negative HBsAg, anti-HIV 1/2, and nonorgan–specific autoantibodies (nuclear, smooth muscle/actin, liver/kidney microsomes, mitochondrial at titers >1/40 by immunofluorescence), with histological diagnosis of chronic hepatitis (CH) with or without cirrhosis. Patients were excluded if they had advanced cirrhosis (large esophageal varices, present or previous history of upper digestive bleeding, ascites, or encephalopathy); hepatocellular carcinoma; cytopenia (platelet counts below 80,000/mm^3 and/or leukocyte counts below 3,000/mm^3); parenteral drug addiction if not abstaining for at least 2 years; alcohol abuse (greater or equal to 80 g/day), unless subjects had stopped for at least 2 years; previous treatment with IFN or other antivirals; and any other contraindications to IFN.

Treatment

All patients received recombinant α2b IFN (Intron-A, Schering Plough, Kenilworth, NJ) at 10 MU tiw for 8 weeks, then 5 MU tiw for the following 18 weeks (total intended dose: 510 MU). At the 26th week, primary responders were randomly assigned to either no further treatment with α2b IFN or to a further 26 weeks of α2b IFN, 5 MU tiw (total intended maintenance dose: 390 MU).

The dose of IFN was reduced to 3 MU tiw when moderate adverse effects and/or tolerable symptoms occurred. If these resolved, IFN was increased again to the intended dose. For severe adverse effects (leukocyte counts below 2,000/mm^3; platelet counts below 50,000/mm^3; creatinine clearance greater than 2.0 mg/dl) and/or intolerable symptoms, therapy was stopped. Decompensation of cirrhosis caused immediate stopping of IFN.

Patients were followed for 1 year after stopping IFN, and biochemical tests (ALT, immunoglobulins, albumin, bilirubin, prothrombin time, and full blood count) were carried out monthly during treatment and follow-up.

Randomization was carried out independently at our institution (University of Palermo) using sealed opaque envelopes. All consecutive patients were offered participation. The study was approved by the Ethical Committee of the institution, and written informed consent was obtained from all patients before starting therapy.

Response Criteria

Treatment efficacy was clinically evaluated by its effect on ALT. Primary response was defined as complete ALT normalization during IFN therapy, on two consecutive observations at least 4 weeks apart, persisting to the end of the 26-week induction period. Any other behavior of ALT was defined as nonresponse, including "breakthroughs" (ALT normalization followed by a new elevation on therapy). Relapse after primary response was defined as any ALT increase after stopping IFN. Sustained response was defined as persistently normal ALT up to 12 months after stopping IFN.

All patients stopping planned treatment at any time either for subjective intolerance or because of side effects were considered withdrawals from IFN therapy. Analysis of results was performed including the latter by intention to treat.

Virological Assessment

Virological tests were undertaken on samples collected during the study and frozen at −30°C. Antibodies to HCV (anti-HCV) were tested on pretreatment sera by EIA and confirmed by immunoblotting (ORTHO EIA2, later EIA3, and RIBA2, Ortho Diagnostics, Raritan, NJ). HCV-RNA was detected in serum by nested polymerase chain reaction (PCR) with primers from the untranslated 5′ noncoding region [Magrin et al., 1992]. Results were expressed qualitatively. The assay detection limit was 10^2 to 10^3 genome equivalents/ml. Sera collected before IFN, at the end of therapy, and at the end of follow-up were analyzed. HCV types were identified by a serotyping immunoenzyme assay [Simmonds et al., 1993] detecting genotype-specific antibodies to epitopes encoded by the NS4 region of the HCV genome (courtesy of Dr. P. Simmonds, University of Edinburgh, UK).

Histological Evaluation

All liver biopsies (Hepafix 1.6 mm needles, Braun Melsungen AG, Germany) were done upon enrollment, and treatment started within 6 months. All specimens were examined by the same pathologist and classified according to standardized criteria [Desmet et al., 1994].

Statistical Evaluation

Sustained response was chosen as the end-point to calculate sample size. Fifty-eight primary responders were needed in each group, assuming a 30% difference in the rate of sustained response between brief (20%) and prolonged treatment (50%), a 5% alpha error, and

a 10% beta error. A 10% excess of inclusions was allowed in order to compensate for withdrawals. Continuous variables were expressed as mean ± standard deviation (SD). Chi-square and Student's *t*-tests were used as appropriate, all *P* values being two-tailed. Multivariate logistic regression was performed in order to identify features useful in predicting primary and sustained response, after adjustment for covariates [Cox, 1970]. The selected predictors were age, sex, disease duration, baseline ALT levels, leukocyte and platlet counts, albumin and gamma globulin levels, prothrombin time, gamma-glutamyltranspeptidase level, (γGT), HCV type, liver structure, and necroinflammatory activity. Disease duration was estimated by the time elapsed in months since the first finding of abnormal ALT levels. The multivariate logistic regression model for sustained response also contained the rate of ALT normalization at 4 weeks after starting IFN, the HCV-RNA status at the end of treatment, and the total intended dose of IFN. Statistical significance was tested by the maximum likelihood approach, and two-tailed values were reported. Regression analyses were done using the PROC LOGISTIC program [SAS, 1988]. Actuarial curves were calculated by Kaplan-Meier's method and analyzed by log-rank test.

RESULTS

The baseline features of the patients in the study are shown in Table I. Males exceeded females in a 2:1 ratio. A history of drug or alcohol abuse was infrequent. Known disease duration was on average about 5 years, but 113 (36.4%) subjects had a recent (≤2 years) onset of illness. All patients were anti-HCV positive. HCV-RNA, tested in 156 cases on pretreatment samples, was always positive. The general features of the subset of cases in which HCV-RNA testing was undertaken were fully comparable to those of the remaining patients. HCV type 1 was found in 225 of 279 (80.6%) patients. HCV types 2 or 3 were found in 11 of 279 (3.9%) cases, while mixed HCV types (1 + 2 in 4; 1 + 3 in 2) were found in 6 of 279 (2.1%). In 37 patients (13.2%) HCV serotyping was impossible because of nonreactivity or nontype-specific results. Cirrhosis was present in 38.3% of cases, while among patients with a noncirrhotic liver structure 85 (27.4%) had fibrosis. Fifty-nine subjects (19%) did not complete the intended schedule because of intolerance or adverse effects.

TABLE I. Baseline Features of All Study Patients*

No. of cases	310
Age (years)	47.8 ± 9.1
M/F	200/100
Previous drug addiction (%)	10 (3)
Previous alcohol abuse (%)	25 (8)
Disease duration (months)[a]	58.2 ± 46.3
ALT (IU/l)[b]	111.3 ± 60.6
Platelets ($\times 10^3$/mm^3)	181 ± 54.3
Leukocytes ($\times 10^3$/mm^3)	6.4 ± 1.6
γGT (IU/l)[b]	47.8 ± 39.8
HCV-RNA positive (%)[c]	156 (100)
Serotype[d]	
Type 1 (%)	225 (80.6)
Type 2 (%)	3 (1.1)
Type 3 (%)	8 (2.8)
Mixed (%)	6 (2.2)
n.r./n.t.s. (%)[e]	37 (13.3)
Liver histology	
Mild chronic hepatitis (%)	140 (45.2)
Moderate/severe chronic hepatitis (%)	51 (16.5)
Chronic hepatitis with cirrhosis (%)	119 (38.3)

*Data expressed as mean ± SD.
[a]Time since the first finding of abnormal ALT.
[b]Normal range: 0-28 IU/l.
[c]Tested in 156 patients.
[d]Tested in 279 patients.
[e]n.r. = nonreactive; n.t.s. = non typespecific.

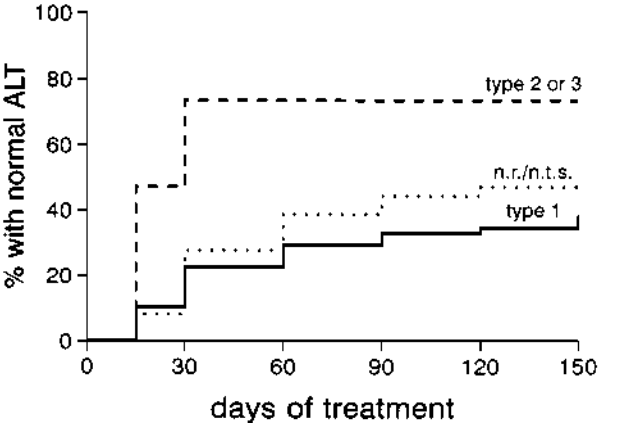

Fig. 1. Effect of HCV type on the kinetics of primary response: type 1 (solid line), type 2 or 3 (broken line), nonreactive (n.r.) or nontype specific (n.t.s.) (dotted line).

Primary Response

One hundred and twenty-four subjects (40%) obtained a primary response. ALT levels normalized in 112 out of 124 cases (90.3%) within 4 months of treatment. Ten patients, after normalizing ALT levels during treatment with 10 MU tiw α2b IFN, had a breakthrough while on 5 MU tiw. Their ALT levels remained abnormal during further therapy and follow-up. Two time-dependent variables (age, disease duration), four disease-related variables (platelet count, γGT level, prothrombin time, presence of cirrhosis), and one virus-related variable (HCV type) were significantly different among primary responders and nonresponders by univariate comparison (Table II). Multivariate analysis (Table III) identified three independent pretreatment predictors of primary response: absence of cirrhosis, low γGT level, and short disease duration. HCV type was just short of significance in this model, due to the relatively small number of subjects infected by non-1 types. The effect of HCV type on the kinetics of response is shown in Figure 1. Patients infected by HCV type 2 or type 3 were significantly more likely to normalize ALT levels within 4 weeks of therapy than those infected by type 1 or nonreactive or nontype specific HCV ($P = 0.003$ by log-rank test).

TABLE II. Main Features of 310 Patients According to Primary Response to IFN*

	Primary responders	Nonresponders	*P*
No. of patients (%)	124 (40)	186 (60)	
Age (years)	46.3 ± 10.5	48.8 ± 7.9	0.02
M/F	82/42	118/68	n.s.
Disease duration (months)	48 ± 40.8	65 ± 48.7	0.001
ALT (IU/l)[a]	113 ± 58.1	109 ± 62.3	n.s.
Platelets ($\times 10^3$/mm^3)	189 ± 52	176 ± 55	0.04
Leukocytes ($\times 10^3$/mm^3)	6.4 ± 1.6	6.5 ± 1.6	n.s.
γGT (IU/l)[a]	38 ± 29.5	54 ± 44.3	0.001
Prothrombin[b]	89.5 ± 10.6	85.8 ± 10.2	0.003
Pretreatment biopsy			
Absence of cirrhosis (%)	97 (78.2)	94 (50.5)	0.0001
Presence of cirrhosis (%)	27 (21.8)	92 (49.5)	
Serotype[c]			
Type 1 (%)	84 (74.4)	141 (85)	0.02
Other types (%)	12 (10.6)	5 (3)	
n.r./n.t.s. (%)[d]	17 (15)	20 (12)	

*Data expressed as mean ± SD.
[a]Normal range: 0–28 IU/l.
[b]Expressed as percentage of control.
[c]Tested in 279 patients (113 primary responders, 166 nonresponders).
[d]n.r. = nonreactive; n.t.s. = nontype specific.

TABLE III. Multivariate Analysis Model for Prediction of Primary Response*

Variable	Score	Beta	Standard error	*P* value	Odds ratio (95% CI)
Structure					
Noncirrhotic	1				
Cirrhotic	0	1.46	0.36	0.0001	4.3 (2.1–8.7)
γGT					
Normal	1				
Abnormal	0	0.63	0.30	0.04	1.9 (1.03–3.4)
Disease duration (months)					
HCV type[a]	Continuous	0.007	0.003	0.04	1.01 (1.001–1.013)
Nontype 1	1				
Type 1	0	1.2	0.66	0.06	3.32 (0.9–12.4)

*Model chi-square 45.8 with 7 DF, $P < 0.0001$, adjusted for HCV type, prothrombin, plaletets, and age.
[a]Nonsignificant.

Sustained Response

After 26 weeks of therapy, the 124 primary responders were randomly allocated to stop treatment (brief therapy group: 64 patients) or to continue IFN therapy (prolonged therapy group: 60 patients). The general features of these two groups were comparable (Table IV). Forty-one subjects (13.2%) had a sustained response, no significant difference being found between the brief therapy group (23 of 64, 35.9%) and the prolonged therapy group (18 of 60, 30%). The timing of post-IFN relapse was comparable between the brief and prolonged therapy groups (Fig. 2). The length of remission under IFN was obviously longer for subjects treated for 52 weeks. All relapses, except five (two brief therapy group, three prolonged therapy group), occurred within 3 months after IFN therapy. Univariate comparison of features of patients with sustained response and relapse is reported in Table V. Multivariate analysis (Table VI) identified four features related to sustained response: negative HCV-RNA at the end of IFN, high baseline ALT values, normal ALT values at 4 weeks of therapy, and a high baseline platelet count.

Virological Results

HCV-RNA was assessed in 156 patients (80 nonresponders, 40 relapsers, 36 sustained responders). At the end of IFN treatment, HCV-RNA was cleared from serum by 55 of 76 (72.4%) primary responders and by 12 of 80 (15%) nonresponders. At the end of follow-up, HCV-RNA was still negative in 32 of 36 (88.9%) sustained responders, in 3 of 40 (7.5%) relapsers, and in 9 of 80 (11.2) nonresponders (Table VII). The rate of sustained clearance of HCV-RNA between the brief therapy group (48.8%) and the prolonged therapy group (42.4%) was closely comparable (*P* = n.s.). Anti-HCV (EIA3) remained positive in all patients with sustained response at the end of follow-up.

TABLE IV. General Features of 124 Primary Responders Randomized to Brief or Prolonged Therapy*

	Brief therapy group	Prolonged therapy group	*P*
No. of patients (%)	64	60	
Age (years)	45.6 ± 10.9	46.3 ± 10.1	n.s.
M/F	39/25	43/17	n.s.
Disease duration (months)	49.3 ± 41.1	47.6 ± 42.1	n.s.
ALT (IU/l)[a]	117.9 ± 62.3	111.3 ± 56.2	n.s.
Platelets ($\times 10^3$/mm^3)	189.3 ± 48.7	187.9 ± 57.2	n.s.
γGT (IU/l)[a]	41.2 ± 31.4	36 ± 28.2	n.s.
Liver histology			
Mild CH (%)	36 (56.3)	35 (58.3)	
Moderate/severe CH (%)	15 (23.4)	12 (20)	
CH with cirrhosis (%)	13 (20.3)	13 (21.7)	n.s.
Serotype[b]			
Type 1 (%)	41 (72)	39 (78)	
Other types (%)	6 (10.5)	6 (12)	n.s.
n.r./n.t.s. (%)[c]	10 (17.5)	5 (10)	
Sustained response (%)	23 (35.9)	18 (30)	n.s.
HCV-RNA negative (%)[d]			
End of therapy	32 (74.4)	23 (69.6)	n.s.
End of follow-up	21 (48.8)	14 (42.4)	n.s.

*Data expressed as mean ± SD.
[a]Normal range: 0–28 IU/l.
[b]Tested in 107 patients (57 brief therapy group, 50 prolonged therapy group).
[c]n.r. = nonreactive; n.t.s. = nontype specific.
[d]Tested in 76 patients (43 brief therapy group, 33 prolonged therapy group).

TABLE V. Main Features of 124 Patients According to Sustained Response to IFN*

	Sustained responders	Relapsers	*P*
No. of patients (%)	41	83	
Age (years)	45.1 ± 11.3	46.4 ± 10.1	n.s.
M/F	32/9	50/33	0.049
Disease duration (months)	46.1 ± 45.8	49.8 ± 39.2	n.s.
ALT (IU/l)[a]	134.2 ± 62.9	103.9 ± 54.6	0.01
Platelets ($\times 10^3$/mm^3)	212.4 ± 53.7	176.9 ± 47.3	0.001
γGT (IU/l)[a]	45 ± 35.5	35.5 ± 26.1	n.s.
Pretreatment biopsy			
Absence of cirrhosis (%)	36 (87.8)	61 (73.5)	n.s.
Presence of cirrhosis (%)	5 (12.2)	22 (26.5)	
Serotype[b]			
Type 1 (%)	25 (64.2)	56 (81.2)	
Other types (%)	7 (17.9)	5 (7.2)	n.s.
n.r./n.t.s. (%)[c]	7 (17.9)	8 (11.6)	

*Expressed as mean ± SD
[a]Normal range: 0–28 IU/l.
[b]Tested in 108 cases (39 sustained responders, 69 relapsers).
[c]n.r. = nonreactive; n.t.s. = nontype specific.

Side Effects and Adverse Reactions

Thirty-five patients (11.3%) stopped treatment because of intolerance or adverse reactions while on 10 MU IFN tiw, and 24 (7.7%) while on 5 MU IFN tiw. Causes and timing of withdrawals are shown in Table VIII. Treatment was stopped more often in patients older than 55 years (25 of 76, 32.9%) than in those younger than 55 years (34 of 234, 14.5%) ($P < 0.001$). Patients with cirrhosis were more prone to stop IFN than noncirrhotics (35 of 119 [29.4%] vs. 24/191 [12.5%], $P < 0.0001$). Eleven patients, all except one with cirrhosis, had a "hepatitic" flare-up (i.e., ALT levels at least 10 times the upper normal values and/or hyperbilirubinemia). None of them developed nonorgan-specific autoantibodies or clinical evidence of autoimmune disease. Hepatitic flares resolved within 3 months after stopping IFN, except in one patient who died of liver failure at 3 months of therapy [Janssen et al., 1993]. None of

TABLE VI. Multivariate Analysis Model for Prediction of Sustained Response*

Variable	Score	Beta	Standard error	*P* value	Odds ratio (95% CI)
HCV-RNA (end of therapy)					
Negative	1				
Positive	0	3.41	1.1	0.001	30.1 (3.3–273)
ALT (before therapy)					
≥4 UNL**	1				
<4 UNL**	0	2.8	0.95	0.005	16.4 (2.5–110)
ALT (at 4 weeks)					
Normal	1				
Abnormal	0	2.78	0.98	0.005	16.4 (2.3–114)
Platelets (before therapy)					
≥140.000/mmc	1				
<140.000/mmc	0	3.45	1.23	0.005	31.5 (2.7–368)

*Model chi-square 45.6 with 6 DF, $P < 0.0001$, adjusted for sex and total dose received.
**UNL = upper normal limits.

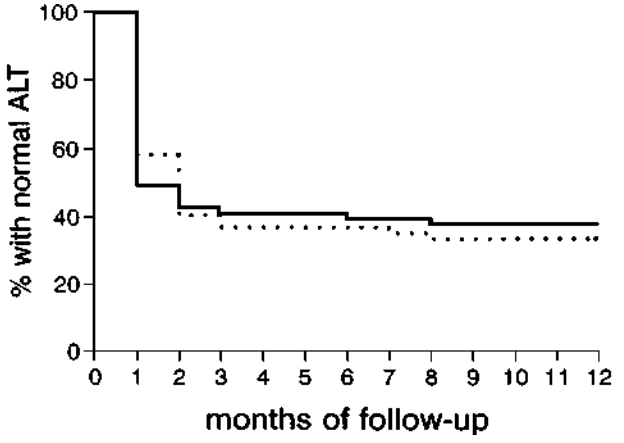

Fig. 2. Rate and timing of post-IFN relapse in primary responders from the brief therapy group (solid line) and prolonged therapy group (dotted line).

these patients normalized ALT or cleared HCV-RNA. Another 25 patients (8.1%) needed a temporary dose reduction for mild side effects.

DISCUSSION

Therapy of chronic HCV infection might be improved by IFN schedules different from the current standard (3 MU tiw for 6 months, i.e., a total dose of 234 MU). The best dose and duration of IFN therapy remain ill defined since most published studies are insufficient for definite conclusions. Recent metanalyses of randomized clinical trials [Poynard et al., 1995a; Niederau et al., 1995] confirm that the current IFN schedule is suboptimal. Niederau et al. [1995] conclude that doses of 3 MU IFN tiw for 6 months are inferior to higher doses and/or longer durations. Poynard et al. [1995b] find that the best efficacy/risk ratio is obtained on a schedule of 3 MU IFN tiw for at least 12 months (468 MU).

In our patients with chronic HCV infection, prolonged high-dose IFN treatment (900 MU over 12 months) did not increase the rate of sustained response in respect to a shorter treatment (510 MU over 6 months). This contrasts with other studies [Saez-Royuela et al., 1991; Chemello et al., 1995; Poynard et al., 1995b] in which a clearcut increase in the rate of sustained response was obtained by prolonging therapy beyond 6 months. Overall, the rate of sustained response in our study was low (13.7%), similar to a 16.7% rate reported by Negro et al. [1994] using 6 MU tiw for 9 months (total dose 702 MU). Poynard et al. [1995b] achieved a sustained response rate of 22% on long-term, low-dose treatment (3 MU tiw for 18 months, total dose 702 MU). By contrast, a higher frequency of sustained response (40–50%) was found in noncirrhotic patients in two randomized clinical trials, in which 351 MU [Jouet et al., 1994] and 660 MU [Kasahara et al., 1995] were given over 12 months. This variability of results could be explained by differences in clinical and virological features (prevalence of cirrhosis, duration of infection, HCV type, viral load) and by the range of schedules of treatment. In particular, our study population shared two important and independent predictive factors of low responsiveness, i.e., presence of cirrhosis (38.3%) and infection with HCV type 1 (80.6%).

In this trial, ALT normalization was mostly achieved within the first 4 months of treatment. No differences in timing of relapse and in the rate of long-term HCV-RNA clearance were seen among patients treated for a short or a long period. HCV-RNA became negative at the end of follow-up in 89% of sustained responders, showing that biochemical and virological end-points are closely related, and that a treatment-induced "healthy carrier" state is infrequent [Garson et al., 1992]. The value of HCV-RNA at the end of therapy in predicting relapse was high. In fact, 90% of primary responders who remained HCV-RNA positive at the end of therapy had a relapse. By converse, a negative HCV-RNA at the end of IFN therapy had a low predictive value for sustained response. Only 62% of primary responders who cleared HCV-RNA became sustained responders. Therefore, testing primary responders for HCV-RNA at 6 months of treatment allows discrimination of viremic subjects, in whom further therapy will not prevent a relapse if a sufficient total dose of IFN has already been

TABLE VII. Clearance of Serum HCV-RNA According to Response in 156 Patients

		Primary responders	
	Nonresponders	Relapsers	Sustained responders
End of therapy (%)	12/80 (15)	21/40 (52.5)	34/36 (94.5)
End of follow-up (%)	9/80 (11.2)	3/40 (7.5)	32/36 (88.8)

TABLE VIII. Patients Stopping IFN Treatment Because of Intolerance or Adverse Effects

	Time of interruption (months)		
	0–2	3–6	7–12
Intolerance	11	1	1
Psychic disturbances	7	5	1
Hepatitis flare-up	5	6[a]	—
Persistent flu-like syndrome	9	—	—
Lichen ruber planus	—	5	—
Cytopenia	1	—	2
Diarrhea	—	1	—
Sepsis	1	1	—
Cardiac arrhythmia	1	—	—
Ascites	—	1	—
Total	35	20	4

[a]One death from liver failure.

given. Alternative treatments, such as IFN/ribavirin combination, should be explored in these patients [Camps et al., 1993b; Kakumu et al., 1993; Koskinas et al., 1995; Schvarcz et al., 1995].

Several multivariate models report an ability to identify patients with increased likelihood of sustained response to IFN [Causse et al., 1991; Pagliaro et al., 1994]. Among pretreatment clinical features, those most predictive of response are the absence of cirrhosis and a short duration of disease. The virological characteristics most consistently predictive of a low likelihood of sustained response are high levels of pretreatment viremia and infection with HCV type 1, especially 1b [Kanai et al., 1992; Chemello et al., 1994; Tsubota et al., 1994; Booth et al., 1993]. Most of these findings were confirmed in our study. Accurate prediction of responsiveness to IFN in the individual patient remains an elusive goal, since the discriminating ability and reliability of these prediction rules are only fair.

An emerging trend favors long periods of treatment, of 12 or even 18 months, aiming to reduce the likelihood of relapse. To reduce the costs of prolonged therapy, low doses of IFN are suggested. Comparisons have mostly been made between low doses for 6 vs. low doses for 12–18 months, showing an advantage for the latter. The total IFN dose, possibly a more important variable than the length of treatment, given by such an approach is similar to that given on more intensive short-term therapy. As an example, 6 months of therapy in the study of Poynard et al. [1995b] amounted to a total dose of about 234 MU, and 18 months to a dose of 702 MU. In our study, subjects treated for 6 months received 510 MU and those treated for 12 months 900 MU. Thus, in respect to the total dose, our short treatment group is not far from Poynard's long treatment group. Our patients might have received within 6 months the optimum amount of IFN in order to minimize relapses. Further therapy up to the 900 MU total dose would not increase in them the likelihood of remaining in biochemical and virological remission. In fact, another study [Chemello et al., 1995] shows that comparable rates of sustained response are obtained by administering a total IFN dose of 468 MU over 6 (28%) or 12 months (31%). The low sustained response rate in our study, as compared to others [Jouet et al., 1994; Kasahara et al., 1995], might be due more to the unfavorable features of patients than to the actual schedule of treatment.

A drawback in the use of a high-dose, short-term approach to IFN therapy would be the low tolerability for some patients. Actually, the withdrawal rate in this trial (19%) was higher than generally reported. We believe that if subjects with cirrhosis and those with older age, most prone to adverse effects and intolerance to IFN, are excluded, the reduced medical and social costs of a shorter period of treatment could make a 6-month, high-dose schedule a reasonable approach for many patients with chronic HCV infection.

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